Electronic Cigarette Research Briefing – February 2019

This research briefing is part of a series of monthly updates aiming to provide an overview of new studies on electronic cigarettes. The briefings are intended for researchers, policy makers, health professionals and others who may not have time to keep up to date with new findings and would like to access a summary that goes beyond the study abstract. The text below provides a critical overview of each of the selected studies then puts the study findings in the context of the wider literature and research gaps.

The studies selected and further reading list do not cover every e-cigarette-related study published each month. Instead, they include high profile studies most relevant to key themes identified by the UK Electronic Cigarette Research Forum; including efficacy and safety, smoking cessation, population level impact and marketing. For an explanation of the search strategy used, please see the end of this briefing.

You can find our previous research briefings at www.cruk.org/UKECRF.

If you would prefer not to receive this briefing in future, just let us know.

Funding call dates

PRC dates

Project Awards – deadline of 23/05/2019 for decisions in late Nov 2019

Postdoctoral Fellowship – deadline of 14/11/2019 for decisions in late July 2020
Contact: PRC@cancer.org.uk

TAG dates

Project Awards – deadline of 29/05/2019 for expressions of interest for decisions in Nov 2019.
Contact: TAG@cancer.org.uk

1. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

- **Study aims**

  This English study randomised 886 adult smokers attending four UK Stop Smoking Services (SSS), to either an e-cigarette starter pack (One Kit) with 18 mg/ml e-liquid or nicotine-replacement therapy (NRT) products of their choice. Both groups received weekly support for at least 4 weeks. Abstinence was measured and biochemically verified at 4, 26 and 52 weeks after quit date. The participants' urges to smoke, respiratory symptoms, and side effects of product use were also recorded.

- **Key findings**

  At 1 year the rate of abstinence was 18% in the e-cigarette group and 9.9% in the nicotine-replacement group (RR=1.83; 95% CI 1.30 to 2.58; P<0.001). Abstinence was also significantly higher in the e-cigarette group at weeks 4 and 26.

  Among those that were abstinent at 52 weeks, 80% were still using e-cigarettes and 9% were still using NRT.

  During follow-up, 3% of those in the e-cigarette group used NRT and 20% of those in the NRT group used e-cigarettes. After excluding these participants who used non-assigned products, the 1-year sustained abstinence rate was 17.7% for those using e-cigarettes and 8% for those using NRT (RR=2.21; 95%CI 1.52-3.22).

  Those using e-cigarettes reported fewer and reduced strength of urges to smoke than those using NRT. Both groups reported fewer respiratory symptoms at 52 weeks compared to baseline. Those in the e-cigarette group reported greater reductions in coughing and phlegm production than the NRT group.

  Those using NRT reported feeling nauseous more often than those in the e-cigarette group (37.9% vs 31.3%). Those in the e-cigarette group reported experiencing throat or mouth irritation more frequently than those in the NRT group (65.3% vs 51.2%). There was no difference between groups in reporting of severe nausea or severe throat or mouth irritation.

- **Limitations**

  The trial only compared e-cigarettes and NRT and did not examine the relative effectiveness of other quitting tools (e.g. prescription medication). Therefore, it cannot give an overall picture of which may be the most effective method of smoking cessation.

  The biochemical validation of smoking cessation could only detect 24-hour abstinence from smoking. Participants may have misreported their smoking status which could bias the results if they were not truly abstinent for the whole follow-up period.

  The participants were only recruited from four UK SSS so might not be representative of the wider smoking population. As participants were enrolled in SSS at the point of recruitment,

they were also likely to be highly motivated to stop smoking which will have affected outcomes, albeit across both groups in the trial.

Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie HJ. (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. N Engl J Med; doi: 10.1056/NEJMoa1808779.

2. Association of Electronic Cigarette Use with Subsequent Initiation of Tobacco Cigarettes in US Youths

- **Study aims**

This US based study surveyed 6,123 children aged 12-15 who reported never having used any tobacco product or e-cigarettes. E-cigarette and tobacco product use was measured over three surveys conducted between 2013 and 2016. The researchers aimed to determine temporal patterns of e-cigarette, cigarette and other tobacco product use (e.g. cigar, pipe, hookah or snus). Analyses were adjusted for demographic factors and other risk factors such as living with a smoker, alcohol use, drug use and susceptibility to cigarette use.

- **Key findings**

There was an increased risk of subsequent ever cigarette use in those that reported using e-cigarettes as their first product (OR=4.09 95%CI 2.97-5.63). This equated to a predicted probability of 13.8% of young people who had used e-cigarettes subsequently trying smoking.

There was also an increased risk of current cigarette use (defined as use in the last 30 days) in young people who reported using e-cigarettes as their first product (OR=2.75 95%CI 1.60-4.73). This equated to a predicted probability of 4.0% of young people who had used e-cigarettes subsequently becoming current smokers.

Young people reporting prior cigarette use had increased risk of ever-using e-cigarettes (OR=3.51 95%CI 2.40-5.14) compared to young people with no prior tobacco use.

When participants were stratified into low-risk and intermediate/high risk groups according to other risky behaviours and cigarette susceptibility, prior e-cigarette users in the low risk group were more than twice as likely to become ever cigarette users (OR 8.57 95%CI 3.87-18.97) than prior e-cigarette users in the intermediate/high risk group (OR 3.51 95%CI 2.52-4.89).

The odds of current cigarette use in prior e-cigarette users in the low risk group was nearly five times higher (OR=10.36 95%CI 3.11-34.54) than those in the intermediate/ high risk group (OR=2.16 95%CI 1.23-3.79).

E-cigarette use was estimated to have contributed to nearly 178,850 individuals trying cigarettes (attributable fraction - 21.8%) in the USA, and an additional 43, 446 current cigarette users (15.3%).

- **Limitations**

  The reference group of this study combined individuals who never used tobacco products or e-cigarettes over the entire survey period with individuals who took up smoking without prior other tobacco product or e-cigarette use. Only 3.3% of the participants reported using cigarettes first, so the majority of this group were never-smokers and are not an appropriate comparison for establishing a gateway effect.

  This study did not assess whether those who had tried e-cigarettes became regular smokers, and likely includes those only experimenting with smoking or e-cigarettes. No conclusions can be made from this study about a causal association between e-cigarette use and regular smoking or vice versa.

  The study assumed that the survey questions used were valid and reliable measures of complex potential confounding factors, such as problem behaviour.

  This study did not control for all possible confounders that could affect results, such as nicotine dependence.

Berry KM, Fetterman JL, Benjamin EJ, Bhatnagar A, Barrington-Trimis JL, Leventhal AM, Stokes A. (2019). Association of Electronic Cigarette Use with Subsequent Initiation of Tobacco Cigarettes in US Youths. JAMA Netw Open; 2(2) doi.10.1001/jamanetworkopen.2018.7794.

3. E-Cigarette use and respiratory disorder in an adult sample

- **Study aims**

  This cross-sectional study surveyed 8,087 people living in Hawaii to examine the association between e-cigarette use, asthma and chronic obstructive pulmonary disease (COPD). The study used the 2016 Behavioural Risk Factor Surveillance Survey (BRFFS), a random dial telephone survey, to collect data on e-cigarette use, cigarette smoking, and respiratory disorders diagnosed by a health professional. Analyses were additionally adjusted for demographics, body mass index (BMI), passive smoking and financial stress.

- **Key findings**

  There was no significant difference in asthma risk between exclusive ever e-cigarette users and those that never used e-cigarettes or smoked (never product users).

  Those who had both smoked and used e-cigarettes were more likely to report an asthma diagnosis compared to never product users (OR= 1.26 95%CI 1.04-1.53). Smokers were also more likely to report an asthma diagnosis (OR=1.27 95%CI 1.10-1.47).

  Exclusive ever e-cigarette users had an increased risk (OR=2.51 95%CI 1.36-4.89) of COPD compared to never product users.

  Smokers and those who had used both cigarettes and e-cigarettes also had an increased risk of COPD (OR=2.58 95%CI 2.34-3.78 and OR=3.92 95CI 2.82-5.44, respectively). There was a

borderline significant interaction between e-cigarette use and smoking for risk of COPD ($p<0.05$).

- **Limitations**

  The study is cross-sectional so cannot establish causality. It's not known when the reported respiratory disorders occurred relative to e-cigarette use, and it's possible that some of the disorders were diagnosed prior to e-cigarette use.

  It's not clear whether the analyses used ever-smoking (smoking more than 100 cigarettes in a lifetime), or current smoking as the smoking variable, which would affect the interpretation of the results.

  Despite collecting data on patterns of e-cigarette use the researchers did not incorporate this into their analysis and the survey did not consider concurrent dual use of e-cigarettes and tobacco separately to consecutive use. Therefore, the results may not give a full picture of any association of e-cigarette use and respiratory disorders.

  This study did not control for all possible confounders that could affect results, such as nicotine dependence or use of other tobacco products.

  The survey was only conducted in Hawaii thus the results may not be generalisable to the wider smoking population.

Wills TA, Pagano I, Williams RJ, Tam EK. (2019) E-Cigarette use and respiratory disorder in an adult sample. Drug Alcohol Depend. doi: 10.1016/j.drugalcdep.

4. Transcriptomic response of primary human airway epithelial cells to flavouring chemicals in electronic cigarettes.

- **Study aims**

  This US study aimed to examine the effects of the flavouring chemicals diacetyl and 2,3-pentanedione on normal human bronchial epithelial (NHBE) cells. Cultured NHBE cells were bathed for 24 hours in solutions of diacetyl (50ppm), 2,3-pentanedione (100ppm) or a control of H_2O. Following exposure, the researchers examined the RNA of the cells to determine changes in gene expression and looked for patterns in affected cell pathways. The researchers also looked at the effect of lower concentrations of diacetyl and 2,3-pentanedione on the most affected genes.

- **Key findings**

  163 and 568 genes were found to be differentially regulated after exposure to diacetyl and 2,3-pentanedione, respectively. Of these, 142 genes were common to both exposure to diacetyl and 2,3-pentanedione.

  6 of the 163 and 4 of the 568 were significantly changed compared to the control. Amongst these, four types of cell pathway were affected by diacetyl and 6 were affected by 2,3-pentanedione. The pathways were related to functions including 'cilium', cilium biogenesis/degradation, cell projection and 'cytoskeleton'. The cilium genes DNAH3 and PROM1 were the two most affected genes.

Diacetyl had a significant effect on DNAH3 at concentrations as low as 5pmm and PROM1 at 2pmm. 2,3-pentanedione had a significant effect on DNAH3 at 25pmm and PROM1 at 10pmm.

After exposure for 48h, the number of ciliated cells was significantly decreased compared to control by both diacetyl and 2,3-pentanedione but the number of goblet cells was not affected.

- **Limitations**

  Cells in this study were exposed to the chemicals in liquid form which may affect gene expression differently to when they are present in e-cigarette vapour. Additionally, the cells were bathed for 24 hours which is far longer than cells would be realistically exposed during e-cigarette use.

  This study only examined the effect of two chemicals and not e-liquid in its entirety, so results cannot be extrapolated to the effects of e-liquid vapour.

  No comparisons to tobacco smoke were made to benchmark the harms of flavourings in e-cigarette liquid. Furthermore, H_2O may not be not a representative background exposure control, as it does not represent regular exposure to air by cells in the lungs.

  As of May 2016, both diacetyl and 2,3-pentanedione are no longer permitted as ingredients in e-liquid in the EU, so the results would not be applicable to those countries.

  Whilst studies in cells provide a basis for potential mechanisms of harm, they are not able to assess real-world exposure to e-cigarette vapour and any actual impact in vivo.

Park HR, O'Sullivan M, Vallarino J, Shumyatcher M, Himes BE, Park JA, Christiani DC, Allen J, Lu Q. (2019) Transcriptomic response of primary human airway epithelial cells to flavouring chemicals in electronic cigarettes. Sci Rep 9(1). doi: 10.1038/s41598-018-37913-9.

Overview

This month we include four papers, three from the USA and one from the UK.

Our first paper reports results from a large randomised controlled trial of e-cigarettes for smoking cessation conducted in England. Funded by NIHR and CRUK, the trial set out to compare the effectiveness of vaping combined with behavioural support from stop smoking services, with Nicotine Replacement Therapy plus behavioural support.

886 smokers accessing services in four areas were randomised to receive the most common form of support that stop smoking services in the UK provide (access to advice and counselling from a trained adviser for at least four weeks and a longer lasting form of NRT (patch) with a shorter-acting form like gum, lozenges or an inhaler) or the same type of behavioural support plus a second generation refillable e-cigarette. The vaping group were initially provided with e-liquid and then informed that they would need to buy their own future supplies, whereas the NRT group received free medication for up to three months. The primary outcome for the study was abstinence from smoking at one year validated by a carbon monoxide breath test. At that point, almost twice as many people had quit in the vaping arm (18%) compared to the NRT arm (10%). Amongst those who

did not quit, some reduced their smoking by at least 50% and this was more common in the vaping arm (13% vs 7%). The vast majority (80%) of people who had quit in the e-cigarette group were still vaping at one year whereas continued use of NRT at one year amongst ex-smokers was rare (9%).

Other researchers have commented on the trials results and methods. Some examples can be found here, here and here. The trial team are continuing to follow up participants. This is important, because previous research has suggested that the risk of relapse after stopping smoking for one year can be as high as 35%. Longer term follow up of trial participants should yield useful data on any differences in relapse to smoking rates between participants in both arms of the study.

Our second study focuses on the relationship between vaping and subsequent smoking using data from just over 6,000 12-15 year olds in the USA. This was a longitudinal survey (the youth arm of the large US PATH study funded by NIH) drawing on three waves of data from 2013-2016. Previous research has examined vaping and subsequent smoking at one year using PATH youth data, and in this paper focuses on the two year follow up. The main outcomes and measures were ever e-cigarette use at baseline (2013) and current (past 30 day) smoking at wave 3 (2016).

The researchers found that young people who had ever tried vaping at baseline were three times more likely to have smoked at least once in the past month at follow up. This relationship was stronger among young people who were deemed at low risk of smoking, based on measures in the survey. Low risk youth were those who did not report trying alcohol, marijuana or prescription drugs and were also assessed as less likely to engage in sensation-seeking behaviour (frightening things, new and exciting things, unpredictable friends) or find smoking appealing. The researchers concluded that trying vaping can lead to taking up smoking and highlight the importance of regulatory measures to protect young people from trying e-cigarettes. However, owing to the limitations listed above the certainty of a gateway effect cannot be determined based on this study. Other researchers have discussed the strengths and weaknesses of the methods and conclusions of the study, including via published comments on the article on the journal website.

Our third study aimed to explore any relationship between vaping, asthma and COPD and to do so drew on data from a cross-sectional survey of just over 8,000 adults living in Hawaii. The survey asked about a whole variety of health and behavioural issues and contained questions about vaping, smoking and respiratory conditions. The authors conducted statistical modelling to look for associations between smoking and/or vaping and asthma and COPD. The primary outcome of interest was whether the survey respondents had, at any time in the past, received a diagnosis of asthma, COPD, emphysema or chronic bronchitis from a health professional. After controlling for smoking (although it is unclear from the article whether this was past or current smoking or both) and potential confounders, the authors found that being diagnosed with COPD was associated with ever trying e-cigarettes in the total sample, and that being diagnosed with asthma was associated with ever trying e-cigarettes among non-smokers. The authors concluded that using e-cigarettes may be contributing to respiratory disorders particularly among non-smokers. Other researchers commented on the findings and suggested that the results may mean that vaping poses similar asthma and COPD risks as smoking.

This was a cross-sectional study, which means that the methods employed cannot tell us whether vaping causes COPD or asthma. Other key considerations, including that these respiratory conditions commonly develop over many years, that e-cigarettes are relatively new, and that the measure of vaping was ever use, also need to be taken into account. It is also relevant that other research has in fact found improvements in respiratory outcomes for patients with COPD who switch from smoking to vaping.

In this bulletin we aim to include a selection of interesting studies across a range of aspects of e-cigarette research, including studies that receive considerable media coverage, in order to try and examine in more detail the research behind the headlines. One such example from that past month is our fourth paper, also from the USA. The researchers aimed to examine the effects of particular chemicals (diacetyl and 2,3-pentanedione) on cells found in the human airway. These chemicals are described in the article and the press release as widely used in e-cigarette flavours, and indeed in an earlier study from 2015, the researchers found these chemicals present in 90% of the e-liquids they tested in the USA. In the current research, cells were bathed in solutions of diacetyl or 2,3-pentanedione (or water, the control) for 24 hours. Both chemicals altered gene expression in the cells in ways that affect cilia production and function. Cilia play a key role in respiratory health and impaired cilia function is found in people with COPD and asthma. In the media, the findings were interpreted to mean that certain e-cigarette flavours can destroy lung function and cause lung disease.

As we have described before in the bulletin, cell line studies such as these are valuable for exploring how different constituents in e-cigarette liquid, emissions or the component parts of the products themselves affect key biological functions. However, as we outline in our summary above, it is unlikely that exposing cells to these chemicals in experiments such as this accurately replicates what happens in the body when vaping occurs. The experiment also did not compare cell response to these chemicals with exposure to tobacco smoke. Finally, and perhaps most importantly, the two chemicals tested have been banned in Europe for use in e-cigarette liquids since 2016, which was not reported by European media outlets.

Other studies from the last months that you may find of interest:

Youth generated prevention messages about electronic cigarettes.

Characteristics and toxicant emissions of JUUL electronic cigarettes.

Deregulation of Biologically Significant Genes and Associated Molecular Pathways in the Oral Epithelium of Electronic Cigarette Users.

Feeling Hopeful Motivates Change: Emotional Responses to Messages Communicating Comparative Risk of Electronic Cigarettes and Combusted Cigarettes.

Barriers and facilitators to switching from smoking to vaping: Advice from vapers.

School-level electronic cigarette use prevalence and student-level tobacco use intention and behaviours.

Youth and young adult exposure to and perceptions of news media coverage about e-cigarettes in the United States, Canada and England.

State-Specific Patterns of Cigarette Smoking, Smokeless Tobacco Use, and E-Cigarette Use Among Adults - United States, 2016.

Effect of Electronic Cigarettes on the Inner Mucosa of the Craniofacial Region.

Dual use of electronic cigarettes and tobacco in New Zealand from a nationally representative sample.

Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchanges disturbances: results from two randomized clinical trials.

Toxicological comparison of cigarette smoke and e-cigarette aerosol using a 3D in vitro human respiratory model.

It Is About Trust: Trust in Sources of Tobacco Health Information, Perceptions of Harm, and Use ofE-Cigarettes.

A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers.

Young adults report increased pleasure from using e-cigarettes and smoking tobacco cigarettes when drinking alcohol.

Rules about smoking and vaping in the home: Findings from the 2016 international tobacco control four country smoking and vaping survey.

Transcriptomic response of primary human airway epithelial cells to flavoring chemicals in electronic cigarettes.

Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths.

Reasons to use e-cigarettes among adults and youth in the Population Assessment of Tobacco and Health (PATH) study.

The moderating effect of gender on the association between E-cigarette use and smoking status: A cross-sectional study.

A new Classification System for describing concurrent use of Nicotine Vaping Products alongside Cigarettes (so-called "Dual Use"): Findings from the ITC-4 Country Smoking and Vaping Wave 1 Survey t.

Characteristics of nicotine vaping products used by participants in the 2016 ITC Four Country Smoking and Vaping Survey.

E-cigarette use (vaping) is associated with illicit drug use, mental health problems, and impulsivity in university students.

A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy.

Longitudinal analysis of associations between reasons for electronic cigarette use and change in smoking status among adults in the Population Assessment of Tobacco and Health Study.

Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA.

Where Do Vapers Buy Their Vaping Supplies? Findings from the International Tobacco Control (ITC) 4 Country Smoking and Vaping Survey.

PRICES, USE RESTRICTIONS, AND ELECTRONIC CIGARETTE USE - EVIDENCE FROM ITC US OF THE 4CV1 (2016) SURVEY.

Electronic cigarette liquid exposure induces flavor-dependent osteotoxicity and increases expression of a key bone marker, collagen type I.

Awareness of changes in e-cigarette regulations and behaviour before and after implementation: A longitudinal survey of smokers, ex-smokers and vapers in the United Kingdom.

Longitudinal e-cigarette and cigarette use among US youth in the PATH Study (2013-2015).

Depressive Symptoms and Suicidality in Adolescents Using e-Cigarettes and Marijuana: A Secondary Data Analysis From the Youth Risk Behavior Survey.

Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars.

[Smoking cessation in secondary prevention of acute coronary syndrome: The role of the electronic cigarette].

Electronic cigarette and combustible cigarette use following a campus-wide ban: Prevalence of use and harm perceptions.

Prevalence of awareness, ever-use, and current use of nicotine vaping products (NVPs) among adult current smokers and ex-smokers in 14 countries with differing regulations on sales and marketing of NVPs: Cross-sectional findings from the ITC Project.

"Cloud chasers" and "substitutes": e-cigarettes, vaping subcultures and vaper identities.

Dual cigarette and e-cigarette use in cancer survivors: an analysis using Population Assessment of Tobacco Health (PATH) data.

Prevalence and correlates of dual tobacco use in cancer survivors.

E-Cigarettes Increase Candida albicans Growth and Modulate its Interaction with Gingival Epithelial Cells.

E-cigarettes and Western Diet: Important Metabolic Risk Factors for Hepatic Diseases.

Electronic cigarettes in Italy: a tool for harm reduction or a gateway to smoking tobacco?

Carbon Monoxide and Small Hydrocarbon Emissions from Sub-ohm Electronic Cigarettes.

Support for e-cigarette regulations among Australian young adults.

Vaping Characteristics and Expectancies are Associated with Smoking Cessation Propensity among Dual Users of Combustible and Electronic Cigarettes.

Association of Depression and Suicidality with Electronic and Conventional Cigarette Use in South Korean Adolescents.

E-cigarette use is strongly associated with recent smoking cessation: an analysis of a representative population sample in Greece.

The Relationship between Electronic Cigarette Use with or without Cigarette Smoking and Alcohol Use among Adolescents: Finding from the 11th Korea Youth Risk Behavior Web-based Survey.

First comparative results about the direct effect of traditional cigarette and e-cigarette smoking on lung alveolocapillary membrane using dynamic ventilation scintigraphy.

Search strategy

The Pubmed database is searched in the middle of each month, for the previous month using the following search terms: e-cigarette*[title/abstract] OR electronic cigarette*[title/abstract] OR e-cig[title/abstract] OR (nicotine AND (vaporizer OR vaping OR vapourizer OR vaporiser OR vapouriser))

Based on the titles and abstracts new studies on e-cigarettes that may be relevant to health, the UK and the UKECRF key questions are identified. Only peer-reviewed primary studies and systematic reviews are included – commentaries will not be included. Please note studies funded by the tobacco industry will be excluded.

This briefing is produced by Helen Callard and Sophia Lowes from Cancer Research UK with assistance from Professor Linda Bauld at the University of Edinburgh and the UK Centre for Tobacco and Alcohol Studies, primarily for the benefit of attendees of the CRUK & PHE UK E-Cigarette Research Forum. If you wish to circulate to external parties, do not make any alterations to the contents and provide a full acknowledgement. Kindly note Cancer Research UK cannot be responsible for the contents once externally circulated.